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Update in the Treatment of Severe Sepsis and Septic Shock

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1. Introduction

The mortality rate of severe sepsis and septic shock has remain high and always has been recognized as one of the most common cause of death worldwide. On the other hand, new interventions has been shown to decrease the complications of this syndrome, even reducing the percent of deaths from over 50% to 30-40% in some studies.

In this chapter, we will discuss some of these therapies including the most important studies leading to better outcomes in the treatment of the above condition.

2. Diagnosis

So far there is no definitive test for the diagnosis of severe sepsis or septic shock. When the human body is exposed to an insult, whether caused by bacteria, trauma, burn, or drug overdose, the individual tends to respond differently depending on their health status and the presence or absence of co-morbidities. Despite no specific test available, there are certain findings that lead us to the diagnosis. These include tachycardia, tachypnea, leukocytosis or leucopenia, fever or hypothermia; all of them are basically criterias defining the Systemic Inflammatory Response Syndrome (SIRS). In addition, the presence of altered mental status, hyperbilirubinemia, metabolic acidosis or respiratory alkalosis and thrombocytopenia could also be useful.

Severe sepsis is known as an acute organ dysfunction secondary to infection. When evaluating a patient with this syndrome time becomes our worst enemy. The organism/s responsible for the acute illness should be identified within the first hours. Appropriate cultures should be obtained before antimicrobial therapy is initiated to confirm the presence of infection and proceed with de-escalation of antibiotic therapy after a susceptibility profile is available. Two quantitative blood cultures should be taken and in patients with indwelling catheters for more than 48 hours, at least one blood culture should be drawn through each lumen of the vascular access [1]. When the same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. Quantitative cultures of other body sites, such as urine, cerebrospinal fluid, wounds and /or respiratory secretions should also be obtained if they are considered to be the source of infection. It is important to understand that obtaining cultures before the initiation of

therapy should only be done if not associated with significant delay in antibiotic administration.

Imaging studies might also be necessary to identify the source of infection, especially when the presence of foreign body or drainage is suspected to be the cause of severe sepsis. However, some patients may be too unstable to undergo invasive procedures or be transported outside the intensive care unit. In such cases bedside ultrasound can be useful.

The potential role of biomarkers in the diagnosis of severe sepsis remains unclear. The use of pro-calcitonin level has demonstrated controversial results since it can be altered in patients with an acute inflammatory process other than infection [2]. In the near future, it is expected that rapid diagnostic methods, such as polymerase chain reaction, be available for quicker identification of pathogens and antimicrobial resistance patterns [3].

3. Source control

Source control is known as the rapid diagnosis of the specific body site of infection amenable to proceed with control measures such as abscess drainage, debridement of infected necrotic tissue and removal of a potentially infected device. Possible infectious foci include: intra-abdominal abscess, intestinal infarction and/or gastrointestinal perforation, cholangitis, pyelonephritis, empyema and septic arthritis. Identification of these sites of infection should be within the first six hours of presentation [4,5].

When source control is required minimally invasive interventions should be employed. For example, performing percutaneous drainage rather than surgical intervention of an abscess [6]. If less invasive approaches are inadequate or there is uncertainty about the diagnosis, then more aggressive measures should be considered. When making such decisions the benefits versus risks as well as the patient's preferences and clinician's expertise must be considered [7].

When an intravascular access device has been identified as the possible cause of severe sepsis removal of the device should be done after other vascular access has been established [8,9]. Special attention should be given when the suspected source of infection is a peripancreatic necrosis. Definitive intervention should be delayed until adequate demarcation of viable and non-viable tissue has been made. In this case endoscopic rather than surgical drainage of biliary tree should be considered taking into consideration what represents the least physiologic insult for the patient [10].

4. Antibiotic therapy

Administration of antibiotics is considered as important as establishing a vascular access and giving fluid resuscitation. Therapy should be started within the first hour of recognition of septic shock. In some cases this may require additional vascular access, however this shouldn't represent a delay in the infusion of antibiotics since this has been associated with increased mortality [11, 12]. The choice of empirical antibiotics will depend on patient's history, including drug intolerance, co-morbidities, the clinical syndrome and susceptibility patterns of pathogens in the hospital, community and those that have previously infected the individual. Recently used antibiotics should definitely be avoided.

Another consideration is whether fungal infection with *Candida* species is the cause of sepsis. Risk factors for candidemia include: central venous catheters, total parenteral nutrition, broad- spectrum antibiotics, high APACHE scores (Acute Physiology and

Chronic Health Evaluation II), acute renal failure, prior surgery (particularly abdominal surgery), gastrointestinal perforations and anastomotic leaks [13, 14, 15]. Immunocompromised patients such as those with hematologic malignancies, recipients of solid organ or hematopoietic stem cell transplants and those receiving chemotherapy are also at increased risk of candidemia [16].

All patients with septic shock should be treated initially with broad-spectrum antibiotics to cover the most common or likely pathogens. It has been demonstrated that failure to initiate appropriate therapy against the pathogen that is later identified as the cause of infection is associated with increased morbidity and mortality [17, 18]. Therapy should be re-evaluated on a daily basis for four reasons: to optimize activity, to prevent the development of resistance, and, to reduce toxicity and costs.

Combination therapy should be given to those patients with risk factors for *Pseudomonas* infection and neutropenia, defined as an absolute neutrophil count (ANC) less than 1500. Although clinical evidence has failed to demonstrate that combination therapy produces superior clinical outcome for individual pathogens in a particular patient group, combination therapies do produce *in vitro* synergy against pathogens in some models [19, 20, 21, 22]. The rationale in administering combination therapy for suspected *Pseudomonas* infection is to increase the likelihood that at least one drug will be effective against that strain. This intervention has demonstrated to have a positive effect on outcome [23].

Duration of therapy should not exceed more than three to five days and de-escalation to single therapy should be performed as soon as susceptibility profiles are available. Narrowing the spectrum of antibiotic coverage and reducing the duration of therapy will decrease the possibility that the patient develops superinfections with pathogens or resistant organisms such as *Candida* species, *Clostridium difficile*, or vancomycin-resistant *Enterococcus faecium*. Therapy should be prolonged from seven to ten days in patients with slow clinical response and those who are immunocompromised or have a source of infection that cannot be controlled. If the cause of the clinical syndrome has been confirmed to be of noninfectious etiology, antibiotic therapy should discontinue immediately. This will decrease the likelihood that the patient becomes infected with drug resistant pathogens.

5. Hemodynamic management in severe sepsis and septic shock

Early sepsis signs are very difficult to diagnose, usually with nonspecific presentations. Patient who arrives with an unapparent infection can progress to a lethal form of disease.

In 1992 The Society of Critical Care Medicine Conference consensus defined sepsis as a systemic inflammatory response that includes 2 or more clinical findings: temperature, respiratory rate, heart rate and white blood cell count in the setting of presumed or a documented infection [24].

Severe sepsis is hallmarked by concomitant organ hypoperfusion or dysfunction [25,26,27].

Sepsis induced hypotension is defined as a systolic blood pressure (SBP) < 90mmhg or mean arterial pressure < 65mmhg or SBP decrease >40mmhg or 2SD below normal for age in absence of other cause of hypotension. Septic shock is defined as sepsis induced hypotension persisting despite adequate fluid resuscitation basically requiring vasoactive drugs.

Early recognition of sepsis with integrated approach screening, triggering evidence-based protocolized care, is anticipated to reduce sepsis morbidity and mortality [28]. The Surviving Sepsis Campaign (SSC) provided some of the best clinical evidence for the management of severe sepsis and septic shock.

6. Initial resuscitation

Patients with septic shock often require early and vigorous resuscitation with an integrated approach directed to rapid restoring systemic oxygen delivery and improving tissue oxygenation.

The first priority involves stabilization of the airway and breathing, with supplemental oxygen and if necessary institution of mechanical ventilation.

Second assessment of perfusion should be done (hypotension persisting after initial fluid challenge, blood lactate ≥ 4 mmol/L). Once hypoperfusion is recognized, early restoration of perfusion is necessary to limit secondary organ dysfunction and reduce mortality. During the first 6 hours of resuscitation, the goals should include: Central venous pressure 8-12 mm Hg with a Mean Arterial Pressure (MAP) over 65 mmHg, a urine output ≥ 0.5 ml/kg/hr and finally a Central venous (superior vena cava) or mixed venous oxygen saturation $\geq 70\%$ or $\geq 65\%$ respectively. If SvO_2 is less than 70%, packed of red blood cells (PRBC) are transfused to achieve a hematocrit level of 30%. If central venous pressure, MAP and hematocrit were optimized and $SvO_2/ScvO_2$ remained below 70% dobutamine is recommended to increase cardiac output and oxygen delivery.

The early goal directed therapy has been shown to improve survival for emergency department (ED) patients with severe sepsis and septic shock. This evidence comes from a randomized controlled single center trial that assigned 253 patients with severe sepsis or septic shock to receive protocolized early goal directed therapy during the first 6 hours in ED or to receive standard therapy before admission in ICU. These resuscitation goals reduced the in hospital mortality from 46.5% to 30.5% ($P=0.009$), a 28 days mortality rate ($p=0.1$) and at 60 day ($p=0.3$) [28].

In 2004 the international group experts published first internationally accepted guidelines [29]. Eventually from 2006 to 2007 the group met again to update the guidelines using new evidence [30]. Central venous pressure is currently commonly used as a guide for resuscitation, although there are recognized limitations to ventricular filling pressures estimated as a surrogate for fluid resuscitations [31, 32]. In mechanically ventilated patients a target CVP of 12 to 15 mmHg is recommended to account for impediment of filling due to increased intrathoracic pressure [33]. Other cases to consider higher CVP include increased abdominal pressure and diastolic dysfunction [34].

The MAP is the most powerful predictor of mortality, commonly used as an indicator of perfusion pressure [35]. Current recommended levels are between 60-65 mmHg in view of adequate autoregulation of blood flow to vital organs [36].

Oxygen is delivered to the tissues as a product of cardiac output (heart rate \times stroke volume) and oxygen content (hemoglobin oxygen saturation \times hemoglobin $\times 1.34$) + (partial pressure of oxygen $\times 0.003$). The tissues extract a percentage of the delivered for cellular respiration and the remaining returns to venous circulation. This amount can be measured from pulmonary artery (SvO_2 , mixed venous oxygen saturation) or by central venous circulation (central oxygen saturation). $ScvO_2$ is only measured with a pulmonary catheter. However, the $ScvO_2$ can be obtained by central insertion of the superior vena cava or right atrium. Pulmonary artery catheter for hemodynamic monitoring and mixed venous saturation has not shown any difference in outcome [37, 38] but it is used in selected cases.

The measurement of $ScvO_2$ is 5-6% higher than SvO_2 , but some studies have shown excellent correlation [39, 40]. So basically a targeted SvO_2 has demonstrated better outcome in this population.

7. Fluid therapy

Septic shock is associated with substantial volume depletion and myocardial dysfunction. The ventricular filling pressure is usually low due to an increase in external losses from gastrointestinal or urinary tracts, bleeding, skin surface or internal losses due to exudation or transudation of bloody fluids. This leads to a generalized vasodilatation and peripheral blood pooling, consequently decreasing the intravascular volume. Adequate fluid resuscitation therefore is one of the cornerstones of the management of septic shock. The aim is the restoration of intravascular fluid volume, reestablish effective tissue perfusion, increase cardiac output and systemic oxygen delivery.

The outcomes advantages between crystalloid and colloids solutions continue to remain unsolved. The recent sepsis campaign guidelines cannot recommend one type or another. The Saline versus Albumin Fluid Evaluation (SAFE), a multicenter randomized trial study showed no difference in 28 day all mortality cause, organ dysfunction, duration of mechanical ventilation, day of renal replacement, hospital or ICU length of stay [41].

However, other study compared 10% pentastarch (a low molecular weight hydroxyethyl starch) with ringer's lactate and the first therapy was associated with higher rates of renal replacement therapy [42].

As the volume of distribution is much large for crystalloids than for colloids, the use of crystalloids for resuscitation requires more fluid and infusion periods to achieve comparable hemodynamic endpoints. Though less colloid is requires, volume expansion with colloid is more expensive. The fluid challenge in patient with suspected hypovolemia may be give at rate of 500-1000ml of crystalloids or 300-500ml of colloids over 30 min and repeated on response (blood pressure, heart rate, urine output) and tolerance (evidence of intravascular fluid overload).

Since the validation of CVP measurements in patients with sepsis is widely debated, other methods has emerged to assess fluids responsiveness. Echocardiography can be use to estimate Left ventricular End Diastolic volume but it is skill operator dependant [43]. Pulse Pressure Variation (PPV) during pressure breath can be used to predict responsiveness cardiac output to change preload [44]. PPV in mechanical ventilated patient is useful for assessing preload responsiveness [45].

Other controversial topics are the fact that excessive amount of fluid may be harmful to the patients with septic shock. Multiple studies have correlated positive fluid balance with reduces survival in ARDS [46] and sepsis [47]. Other study of 87 patients in mechanical ventilation showed that positive fluid balance were associated with failure of spontaneous breathing trials [48].

A prospective study, The Fluid and Catheter Treatment Trial (FACTT) randomized 1,001 patients with acute lung injury or ARDS to conservative (CVP < 4mm Hg or pulmonary artery occlusion pressure [PAOP], < 8mm Hg) vs. liberal (CVP, 10 to 14 mmHg, or PAOP, 14 to 18mm Hg) fluid management and concluded that there was no mortality difference at 60 days, but the conservative fluid strategies improved lung function, ventilator free days and reduce ICU length of stay [49].

A new retrospective study review from the Vasopressin in Septic shock trial (VASST) in which was analyzed the positive fluid balance and determined correlation with CVP at 12hrs and during subsequent days. The study found increase mortality with positive fluid balance early in resuscitation and cumulative for 4 days. The CVP may be use as a gauge to fluid balance < 12hrs, but becomes an unreliable marker of fluid balance thereafter. The overall data suggest

the optimal survival occurred at CVP of 8mmHg and positive fluid balance of 3 l during first 12hr; however a randomized control studies is necessary to prove this [50].

The approach of fluid resuscitation in sepsis shock patients suggest that should be liberal in the first 6h of acute resuscitation, guided by Svo₂ or Scvo₂. Once the patient is adequately resuscitated, fluids should be hold without the necessity of maintenance therapy. The intravascular status should be continuing monitoring with physical examination with observation of sign of hypoperfusion, weight, input and output chart and other measures [51].

8. Vasoactive therapy

When the fluid administration fails to restore an adequate arterial pressure and organ perfusion , a vasoactive agent should be started. The ultimate goals are to restore effective tissue perfusion and normalize cellular metabolism.

In shock state, the estimation of blood pressure using a cuff may be inaccurate and the use of arterial catheterization provides more precise and reproducible measurements of arterial pressure [52].

Most experts recommend a MAP \geq 65 mm Hg.

9. Norepinephrine

Norepinephrine is the endogenous mediator of the sympathetic system having a strong α -adrenergic activity with less β -adrenergic effects. It increases MAP by vasoconstriction, with small (10-15%) increase in cardiac output and stroke volume [53-58]. Filling pressure is either unchanged [59] or modestly increased (1-3 mm Hg) [54-57].

In open labels trials, norepinephrine at doses ranges 0.01 to 3.3 μ g/kg/min has demonstrated to increase MAP in patients who remained hypotensive after fluid resuscitation and dopamine [54-56, 58, 60, 64-65].

A randomized trial compared vasopressor agents in 32 resuscitated septic patients in which either dopamine or norepinephrine were given to keep hemodynamic derangements. Dopamine was successful only in 31% vs. 93% treated with norepinephrine [63].

Another larger multicenter randomized trial study, which compared dopamine vs. norepinephrine for treatment for any kind of shock (cardiogenic, hypovolemic, septic), found no significant death rate at 28 days. However, there were more arrhythmic events among patients treated with dopamine. Also, patients who suffered cardiogenic shock and were managed with dopamine had an increase mortality rate at 28 days. This and other studies suggested that norepinephrine is a safer drug in cardiogenic shock and myocardial infarction patients due to tachyphylaxis [67].

Other important multivariate analysis included 97 septic shock patients and was statistically significant for a reduced mortality by the use of the norepinephrine. The use of high dose dopamine, epinephrine or dobutamine had no significant effect [68].

The studies of norepinephrine with splanchnic blood flow in septic patient have mixed results. A recent one compared norepinephrine, dopamine and epinephrine for septic shock and there was no significant difference between them [69].

10. Dopamine

Dopamine has predominantly β -adrenergic effects in low to moderate dose ranges (up to 10 μ g/kg per minute). Higher doses cause α -adrenergic predominance leading to arterial vasoconstriction and increase blood pressure.

It may be useful in patients with decrease systolic dysfunction but causes more arrhythmias than norepinephrine [70]. Although it has shown diuretic properties, it is not recommended for above purposes [71] probably due to its neuroendocrine effects, which may interfere with prolactin, thyroid, pituitary function and some of the immunosuppressive functions [72-73].

Moreover, the use of Dopamine at "renal dose" has been discouraged due to ample evidence in meta-analysis and high quality prospective trial. An important one included 328 critically ill patients with early renal dysfunction and were separated in groups for low dose dopamine or placebo. No difference was found in the primary outcome (peak serum creatinine level, need for renal replacement and urine output). Other variables such as survival or hospital length of stay were unremarkable as well.

Multiple recent studies have shown more detrimental effects with Dopamine. For example, the use of dopamine was associated with an increased mortality in patients with shock in a prospective multicenter observational study of 198 European ICUs [74].

In conclusion, many experts have recognized that Dopamine should not be the first vasoactive drug in patients in shock and some of them recommended that should not be used anymore in patients with septic shock.

11. Epinephrine

Epinephrine has potent β_1 - β_2 and α_1 -adrenergic activity, although the elevated MAP in sepsis comes mainly from an increase in cardiac output [75]. The major concerns in use of epinephrine are: higher myocardial oxygen demand, hyperglycemia, increased lactate levels and a reduction in regional blood flow [76-79].

Myburgh and colleagues performed a prospective multicenter, double blinded and randomized control trial in 280 ICU patients comparing epinephrine to norepinephrine finding no difference in the time to achieve arterial pressure goals, 28 day mortality, 90 day mortality. However, 13% of the patients in the epinephrine group were withdrawn from the study because of lactic acidosis or tachycardia [84].

Another randomized control trial conducted by Annane and colleagues compared 330 patients with septic shock and evaluated the efficacy of norepinephrine with or without dobutamine against epinephrine alone [85]. They found that there was no difference in efficacy or safety between the two groups. For instance, epinephrine is not currently recommended as first line vasopressor therapy in view of concerns about tachyarrhythmias and its effects on gastric perfusion.

12. Phenylephrine

Phenylephrine works at the α_1 receptors causing increased blood pressure by vasoconstriction. Its use in septic shock has had controversial results but so far there has been only a few related studies.

In comparison with norepinephrine, phenylephrine reduces splanchnic blood flow, oxygen delivery and lactate uptake [86]. On the other hand, it may be a good option when tachyarrhythmias limit therapy with other vasopressors.

13. Vasopressin

Arginine-vasopressin is an endogenous hormone that is released in response to decreased intravascular volume and increased plasma osmolality. Vasopressin constricts vascular

smooth muscle through V1 receptors. It also increases the responsiveness of the vascular bed to catecholamines [87,88]. Vasopressin may also increase blood pressure by inhibiting vascular smooth muscle nitric oxide [89] production and K⁺-ATP channels [90].

A newer interest has emerged as an additive vasoconstrictor in patients with septic shock resistant to catecholamines [90]. Vasopressin have been found to be in lower levels than expected in patients with septic shock, suggesting relative deficiency. Its combination with norepinephrine increases the splanchnic flow and urinary output [91]. Several small-randomized studies comparing vasopressin with norepinephrine have demonstrated that initiation of it decreases catecholamine requirements [92].

A large, multicenter, randomized trial (VASST) [97] with 778 patients was done to determine whether norepinephrine and vasopressin decreases mortality compared with norepinephrine alone. No difference was found in mortality, ICU or hospital length of stay, discontinuation of vasopressors or organ dysfunction. The use of norepinephrine infusion was significantly lower in cases with vasopressin dose of 0.03U/min, but vasopressin seems to be better in less severe group. New retrospective analysis of the VASST suggests a beneficial effect between vasopressin and corticosteroid in patients with septic shock that were also treated with steroids. Patients with vasopressin with corticosteroids have significantly increased in plasma vasopressin levels. Vasopressin at 0.03u/min added to norepinephrine seems to be as safe as effective as norepinephrine in fluid resuscitated patients with septic shock.

14. Dobutamine

Is an inotrope that has variable effects on blood pressure due to β_1 and β_2 adrenergic agonist effect resulting in an increase heart rate and cardiac contractility. Dobutamine should be considered in patients who have low cardiac output in the presence of adequate ventricular filling pressures and appropriate mean arterial pressure [28-29].

In septic patients, it increases oxygen delivery and consumption. As part the early goal directed therapy dobutamine was associated with significant absolute reduction in mortality [28].

An inotrope should be considered to maintain an adequate cardiac index, mean arterial pressure, mixed venous oxygen content and urine output. Other available agents includes phosphodiesterase inhibitors such as milrinone and enoximone, and calcium sensitizers such as levosimendan. There are currently inadequate data to recommend them in septic shock.

15. Severe sepsis/septic shock and the use of steroids

Sepsis syndrome is characterized by having a disequilibrium between pro-inflammatory and anti-inflammatory cytokines leading to overproduction of IL-1, IL-6 and TNF- α from the lymphocytes, macrophages and endothelial cells [100]. It is known that TNF- α and IL-6 decreases cortisol levels from the adrenal gland and ACTH production from the pituitary gland resulting in secondary adrenal insufficiency in approximately 16.3 to 55% of patients [101]. Systemic steroids might then have a beneficial role by inhibiting pro-inflammatory cytokines, nitric oxide and phospholipase A2 [102]. They also enhance the activity of adrenergic receptors and increased myocardial contractility resulting in improvement of hemodynamics response.

Hydrocortisone is usually the steroid of choice because it is the synthetic derivative of cortisol and also has intrinsic mineralocorticoid activity. After the study by Schumer, a short

course of high-dose corticosteroids became an accepted therapy [103]. Subsequent studies, however, did not confirm a survival benefit with this regimen and suggested an increase in superinfection-related mortality were patients went from being immunomodulated to being immunosuppressed.

Multiple randomized trials in patients with septic shock confirm that low-dose steroid therapy in these patients improves blood pressure, thereby, causing reduction in vasopressor support.

In 2002 Annane demonstrated a reduced mortality ($p=0.04$) in a subgroup of patients that were non responders to an adrenocorticotropic hormone tests (ACTH test) but the mortality rate was increased ($p=0.96$) in patients without evidence of relative adrenal insufficiency (responders) [104]. In 2008 Russell found out a reduced mortality in a subgroup of patients with severe septic shock in those receiving steroids and vasopressin versus norepinephrine and steroids raising the concern that vasopressin may increase the levels the intrinsic cortisol levels [105].

Bauer found a positive interaction of vasopressin and corticosteroids in a nonrandomized cohort study of patients with septic shock, all of whom received vasopressin. Patients who received corticosteroids and vasopressin had lower mortality rates (47.6% vs. 80.9%; $p = 0.02$) compared with patients who did not receive corticosteroids with vasopressin. Furthermore, a randomized, blinded, placebo-controlled trial ($n = 100$) of vasopressin plus corticosteroids or placebo in human cardiac arrest found a beneficial interaction of vasopressin and corticosteroids. Patients who received vasopressin plus corticosteroids had more frequent return of spontaneous circulation (81% vs. 52%; $p = .003$) and higher survival rates (19% vs. 4%, $p = .02$) than patients who received vasopressin plus placebo.

Finally a multicenter, randomized, double-blind, placebo-controlled study called Corticosteroid Therapy of Septic Shock (CORTICUS) study, evaluated the efficacy and safety of low-dose hydrocortisone therapy in a broad population of patients with septic shock [106]. The use of low-dose hydrocortisone had no significant effect on the rate of death in 251 patients with septic shock versus placebo at 28 days, regardless of the patients' adrenal responsiveness to corticotropin. The proportion of patients in whom reversal of shock was achieved was similar in the two groups, though this goal was achieved earlier in patients who received hydrocortisone. On the basis of these findings, hydrocortisone cannot be recommended as general adjuvant therapy for septic shock (vasopressor responsive), nor can corticotropin testing be recommended to determine which patients should receive hydrocortisone therapy. Hydrocortisone may have a role among patients who are treated early after the onset of septic shock who remain hypotensive despite the administration of high-dose vasopressors and adequate fluid resuscitation.

16. Activated protein C and its role in severe sepsis/septic shock

Sepsis is associated with alterations in the blood coagulation, fibrinolytic systems and inflammatory pathway. This leads to disorders of tissue perfusion that generate multiple organ system failure with depletion of platelets and coagulation factors along with the activation of natural inhibitors of coagulation. Activated protein C (APC), an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation, is an important modulator of the coagulation and inflammation associated with severe sepsis [107]. It is converted from its inactive precursor, protein C, by thrombin coupled to thrombomodulin. The conversion of protein C to activated protein C may be impaired

during sepsis as a result of the down-regulation of thrombomodulin by inflammatory cytokines. Reduced levels of protein C are found in the majority of patients with sepsis and are associated with an increased risk of death.

A randomized, double-blind, placebo-controlled, multicenter trial was conducted with recombinant human activated protein C in 1998 in 1690 patients to evaluate mortality at 28 days [108]. The PROWESS (Protein C worldwide evaluation in severe sepsis) trial was completed in 2001 and statistical analysis indicated a decreased 28th mortality rate of 30.8% in the placebo group compared with 24.7% in the drotrecogin alfa group. The difference in the mortality was limited to patients with a higher risk of death, that is, APACHE II scores > 25. In these groups mortality was reduced from 44% in the placebo group to 31% in the treatment group. Efficacy was doubtful in patients with low risk for death and serious bleeding was higher in the APC group.

In 2005 the ADRESS trial evaluated the efficacy of APC in patients with APACHE score < 25 or single organ failure and there was no difference in mortality among both groups at 28 days [109].

There is increased risk for serious bleeding and no beneficial effect in those patients with low risk for death, such as those with single organ failure or an APACHE II score less than 25 [110].

More recently a Cochrane database submitted their review on APC and again no difference in mortality was observed in approximately 4434 adults with sepsis. Increased risk for serious bleeding was noted and for this reason a new trial was requested by the FDA that should be completed at the end of 2011.

On the basis of this findings APC is recommended for patients with severe sepsis and high risk for death if there is no contraindications.

17. Glucose control in ICU

Blood glucose control was originally investigated in the setting of diabetes because uncontrolled levels seemed to predisposed to multiple infections (e.g., cellulitis, postoperative wound infections). Although the exact pathogenesis was unknown, it was speculated that the increased risk of infection was related to decreased cellular immune function [111]. Later studies (both in animals and humans) demonstrated that the depressed ability to fight off infection was a result of impaired polymorphonuclear leukocyte function, chemotaxis, and phagocytosis.

Extensive observational data have shown a consistent, almost linear relationship between blood glucose levels in hospitalized patients and adverse clinical outcomes, even in patients without established diabetes [112].

Van den Berghe reported a dramatic 42% relative reduction in mortality in the surgical ICU when blood glucose was normalized to 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter) by means of insulin infusion in a prospective, randomized fashion [113]. Five years later, the same investigators reported findings from their medical ICU, revealing no mortality benefit from intensive glucose control, except in a subgroup requiring critical care for 3 or more days [114].

A parallel-group, randomized, controlled trial involving adult medical and surgical patients admitted to the ICUs of 42 hospitals was conducted from December 2004 through November 2008 to evaluate mortality in patients assigned to tight glucose control versus conventional glucose control (NICE SUGAR Trial)[115]. Ninety days after randomization,

829 of 3010 patients (27.5%) in the intensive-control group had died, as compared with 751 of 3012 patients (24.9%) in the conventional-control group. Severe hypoglycemia was significantly more common with intensive glucose control. In the basis of this findings, glucose control with intravenous insulin should be started in patients with severe sepsis upon stabilization at ICU when glucose levels are above 180 (1B) with a goal blood glucose target in the range of 150 mg/dL (2C). The American Association of Clinical Endocrinologists recommends a glucose range of 140 to 180 mg/dL for most hospitalized persons.

18. Mechanical ventilation in sepsis

The strategies to ventilate patients with severe sepsis have been changing for the last decades. Multiple studies demonstrated that ventilating with the usual tidal volume may have detrimental effects causing what is now recognized as ventilator induced lung injury. This complication have led to new forms of ventilation called lung protective management in which lower volumes are provided in order to prevent alveolar overdistention.

Sepsis itself can induce acute lung injury (ALI) in about 50% of the cases. ALI is defined as an acute onset insult resulting in bilateral radiographic infiltrates, pulmonary artery wedge pressure ≤ 18 mm Hg when measured by a pulmonary catheter, an echocardiogram showing no evidence of left atrial hypertension, and an arterial oxygen tension to fraction of inspired oxygen ratio (PaO₂/FiO₂) of 201 to 300 mmHg. The difference between ARDS is mainly the worsening of hypoxemia having above ratio less than 200 mmHg [116].

With conventional ventilation, patients with ARDS had higher mortality rate when used prior the new recommendations. Lung protective ventilation has shown a decrease mortality rate and ventilator-induced lung injury [117]. This intervention also know as low tidal volume ventilation involved an initial tidal volume of 6 ml/kilogram of predicted body weight (PBW) aiming for a plateau pressure of ≤ 30 cm H₂O. If plateau pressure remains > 30 after reduction of tidal volume, it should be reduced further to as low as 4 ml/kg PBW [118]. In contrast to the conventional ventilation that involved a tidal volume of 12 ml/kilogram of body weight with low positive end-expiratory pressure (PEEP), protective ventilation avoids alveolar overdistention and end-expiratory collapse [119]. The titration of the PEEP should approach a balance between lung recruitment and overdistention, barotrauma, and hypotension in order to maintain adequate oxygenation (arterial oxygen saturation over 88%). This permit lower FiO₂, decreasing the risk of oxygen toxicity. High PEEP level may increase airway pressures and lung volumes, which could contribute to ventilator induced lung injury from overdistention [120]. The optimal strategy to set PEEP has not been established [118,120,121].

The low tidal volume ventilation can result in respiratory acidosis which now is known as permissive hypercapnia. The respiratory rate is usually increased to keep adequate minute ventilation. The increase on carbon dioxide can cause vasodilation, increase in heart rate, cardiac output, blood pressure, pulmonary vascular resistance and decrease renal blood flow; but modest hypercapnia has been demonstrated to be safe in clinical trials. This ventilation is allowed in order to prevent pulmonary overdistention and consequently negative effect in ALI/ARDS [122]. If severe respiratory acidosis, pH < 7.15 , develops the infusion of sodium bicarbonate may be considered. These type of ventilation is contraindicated in patients with cerebral disorders such as cerebrovascular insults, trauma, or space-occupying intracranial lesions because it may increase the intracranial pressure.

In patients with refractory hypoxemia, prone position ventilation has been recommended despite no benefits in survival. Proper precautions should be taken to avoid complications like pressure sores, accidental dislodgment of the endotracheal tube and central venous catheters [118]. Same results has been noticed in studies with high frequency oscillatory ventilation and Extra Corporeal Membrane Oxygenation (ECMO).

Noninvasive ventilation (NIV) has been suggested in patients with ALI/ARDS since it allows better communication, reduces incidence of infection, requirements for sedation and duration of intensive care unit stay [124]. Its use should be considered only in hemodynamically stable patients who are cooperative, able to protect the airway and spontaneously clear the airway of secretions; and who are anticipated to recover rapidly from the precipitating insult [124]. Continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV) are the most commonly used modes. In NIPPV, two different pressures are used: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), whereas CPAP maintains a constant positive airway pressure throughout the respiratory cycle. NIPPV may confer an advantage over CPAP by reducing the work of breathing during inspiration by providing additional inspiratory pressure. The main goal of NIV in patients with ALI/ARDS includes improvement of hypoxemia, to unload the respiratory muscles and eventually relieve dyspnea. A practical approach has been postulated, it should be use judiciously in selected patients to prevent decrease in survival if intubation is delayed [124].

The discontinuation of mechanical ventilation crucial and should be base on weaning protocol to assess readiness of successful extubation, reducing the duration and the complications related to it [118].

19. Sedation, analgesia, and neuromuscular blocked in sepsis

Patients critically ill with sepsis usually require control of anxiety, agitation and pain, especially when they are with mechanical ventilation support. There are several options of sedative-analgesic medications including benzodiazepines, opioids and neuroleptics. The intention is to achieve adequate comfort and safety using protocols with a sedation goal [125].

This accomplishment should be use according to the patient clinical condition. Several scoring scale has been validated, none superior to the other; Riker Sedation-Agitation Scale (SAS), Motor Activity Assessment Scale (MAAS), Minnesota Sedation Assessment Tool (MSAT), and Richmond Agitation-Sedation Scale (RASS) and Ramsay Sedation Scale [126].

The use of protocol-directed sedation can reduce the duration of mechanical ventilation, the intensive care unit and hospital lengths of stay, and the need for tracheostomy [127]. The use of the combination of spontaneous awakening trials (SATs), daily interruption of sedatives, with spontaneous breathing trials (SBTs) for the management of mechanically ventilated patients in intensive care results in better outcomes. It can also decrease mechanical ventilation, intensive care and hospital stay with survival improvement [128].

The pain management should be assessed frequently using a pain scale appropriate to patient's condition. The numeric rating scale has been recommended in critical ill patients because it is easier to apply [126]. Patients who cannot communicate behavioral pain scale (BPS) may be used. The pain intensity is evaluated by facial expression, movement of the upper extremities and compliance with ventilation [129].

The neuromuscular blocking agents (NMBAs) are not recommended, when possible, in septic patients due to prolonged neuromuscular blocked following discontinuation [125].

They should be used when appropriate sedation and analgesia cannot be achieved. The indications are to facilitate mechanical ventilation, improving chest wall compliance, preventing respiratory dys-synchrony, reducing peak airway pressures and decrease oxygen consumption by reducing work of breathing (1, 6). Patients receiving NMBAs should be assessed both clinically and by train-of-four monitoring, a peripheral nerve stimulation test, with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches from a scale of 0 to 4. This may reduce clinical recovery delay from NMBAs [125,130]. The administration of NMBAs in early ARDS was demonstrated to improve outcomes, it can decrease duration of mechanical ventilation, hospital stay and ventilation induce lung injury. Further studies are required before this clinical practice can be adopted [131].

The 'ABCDE' bundle has been proposed combining evidence-based interventions. It consists of A waking and Breathing trial coordination, Choice of sedatives and analgesics, Daily delirium monitoring, Early mobility and exercise to improve the management of mechanically ventilated patients [132].

20. Acute kidney injury and sepsis

Acute kidney injury (AKI) is a common complication of sepsis and septic shock. Approximately 35 to 50% of the cases in the ICU can be attributed to sepsis [133]. Patients with sepsis related AKI have higher hospital mortality, 74% compared with a 45% due to other diagnosis [134]. If renal replacement therapy is required the mortality rate rises further to as high as 80% [135].

The diagnosis of acute kidney injury, previously termed acute renal failure, is based on an elevation in the serum creatinine (SCr) levels. Many definitions have been proposed throughout the years since there was no real consensus on the degree of elevation required for the diagnosis of AKI. Because of this variability there was the need to develop a classification system that could propose a uniform definition within the medical community.

The Acute Dialysis Quality Initiative's "RIFLE" (Risk, Injury, Failure, Loss, ESRD) criteria was first established and included five categories, the first three of which define AKI and its severity largely by percentage increases in SCr over baseline [136]. The Acute Kidney Injury Network (AKIN) criteria was then proposed and [137] includes three stages, the last two of which are identical to the RIFLE criteria. Both definitions also incorporate severity and duration of oliguria as alternative criteria.

An improvement in urine output is a sensitive indicator of AKI, with an oliguric AKI associated to a poorer prognosis. Documentation of urine volume should be of general practice in the management of any acutely ill patient, especially those with sepsis or septic shock.

21. Renal replacement therapy

The decision to start renal replacement therapy (RRT) in patients with AKI should be based on the clinical aspects after careful evaluation of fluid, electrolyte and metabolic status of each individual patient.

Currently there are no evidence-based guidelines to suggest an optimal time to initiate treatment; it continues to be a clinical decision after the diagnosis of AKI is confirmed and before overt complications develop.

22. Continuous Renal Replacement Therapy (CRRT) vs. Intermittent Hemodialysis (IHD)

Intermittent hemodialysis-associated hypotension is estimated to occur in approximately 20–30% of treatments. Some of the causes are dialysis specific, such as excessive or rapid volume removal, changes in plasma osmolality, autonomic dysfunction, and anaphylactic membrane reactions [138]. CRRT is most frequently used in patients who are hemodynamically unstable, usually because of sepsis or severe cardiac dysfunction because it closely resembles normal physiologic renal function with slow correction of metabolic derangements and slow fluid removal. Despite this there is no clear evidence to support the superiority of either technique, regarding mortality in the ICU. Clinicians should choose a technique according to individual patient characteristics, nursing proficiency, and technical resources.

23. Sodium bicarbonate replacement in sepsis

Infusions of sodium bicarbonate long have been advocated to correct persistent metabolic acidosis. It was said to result in increased pH with less cellular dysfunction, improved cardiac contractility and the activity of vasopressor agents. However clinical studies suggest that this therapy should be tried as a last resort to improve the patient's clinical status.

In a recent review [139] the data supporting sodium bicarbonate infusion were evaluated. It seems clear from animal data that artificially increasing the pH does not improve such parameters as cardiac function or weaning of vasopressor agents. Further decrease in serum pH levels is possible since sodium bicarbonate is converted to carbon dioxide and water, which can also lead to sodium and fluid overload. Sodium bicarbonate replacement should be considered as a last resource and is not recommended in patients with hypoperfusion induced lactic acidemia with pH > 7.15 .

24. Venous thromboembolic events prophylaxis

Patients with severe sepsis have higher risk of venous thromboembolic events (VTEs) due to one or more risk factors, including advanced age, chronic cardiopulmonary disease, recent surgery, immobilization, in-dwelling vascular catheters, and previous VTE history [140]. Sepsis is associated with systemic activation of coagulation and frequently results in disseminated intravascular coagulation (DIC) [141]. Also hypoperfusion and reperfusion seen in patients with shock has been associated with endothelial damage. Indeed, VTE prophylaxis using unfractionated heparin (UFH), low molecular weight heparin (LMWH), and/or mechanical methods has become standard of care in most institutions [142].

25. Stress ulcer prophylaxis

Stress ulcers are a common complication in ICU admissions and more importantly in those related to sepsis. A clear etiology has not been established but ischemia and reperfusion are thought to cause the mucosal defenses to break down, resulting in mucosal injury and ulceration [143]. During sepsis and septic shock, reduced blood flow, hypoperfusion, and reperfusion injury may be seen secondary to hypotension or hypovolemia. These are the most common risk factors contributing to mucosal injury, hence leading to development of stress ulcers.

Treatment options include H₂ receptor antagonists (H₂Ras) which act by decreasing gastric acid secretion through reversible, competitive inhibition of histamine-stimulated acid secretion and are effective in reducing basal acid production. However, because gastrin and acetylcholine provide alternative pathways to the stimulation of acid secretion, acid suppression with H₂RAs is incomplete.

Proton pump inhibitors (PPIs) inhibit the final step in acid production, the generation of gastric hydrogen ions via hydrogen potassium adenosinetriphosphatase; they provide long-lasting suppression of acid secretion.

Both H₂Ras and PPIs have been proved effective for prevention of stress ulcers and superiority of one treatment option over the other has not been clearly established in clinical trials. Careful considerations must be taken on greater incidence of ventilator associated pneumonias on patients with sepsis already placed on mechanical ventilation, due to an increase in stomach pH. Physicians most weight individual risk over benefits, especially in those patients at greater risks of developing gastrointestinal bleeding.

26. References

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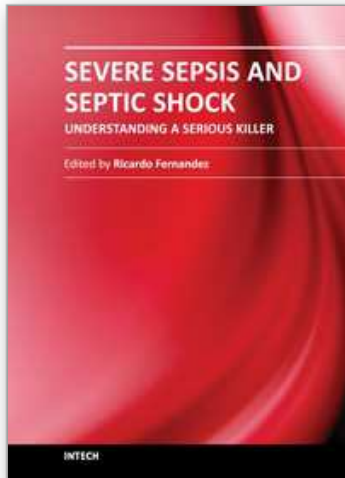
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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease. We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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